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| EXAMINER | |
|---|---|
| SCHNIZER, RICHARD A | |
| **ART UNIT** | **PAPER NUMBER** |
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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/742,892 | GAULDIE ET AL. | |
| | Examiner | Art Unit | |
| | Richard Schnizer, Ph. D | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,4-14,17-19 and 21-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-14,17-19 and 21-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 December 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

An amendment and an appeal brief were received and entered on 6/24/04.

Claims 2, 3, 15, 16, and 20 were canceled as requested.

Prosecution is hereby reopened for the purpose of making a new ground of rejection.

Claims 1, 4-14, 17-19, and 21-25 remain pending and are under consideration in this Office Action.

This Action is Non-Final due to new grounds of rejection for lack of adequate written description and enablement not necessitated by Applicant's amendment.

### *Objections Withdrawn*

After further consideration, the objection to the specification for the introduction of new matter in the Sequence Listing is withdrawn. The specification as filed disclosed three oligonucleotides. The Sequence Listing was amended to reflect this, and the amendment does not introduce new matter.

### *Rejections Withdrawn*

The rejection of claims 1, 4-14, 17-19, and 21-25 under 35 USC 112, first paragraph for new matter is withdrawn in view of Applicant's amendment deleting the new matter.

### *Claim Objections*

Claim 24 is objected to because it contains a typographical error. The word "form" in the penultimate line should be deleted and replaced with the word "from", which was present in the previous version of the claim. This claim has been interpreted as if the word "from" had been used.

### *Specification/Drawings*

The specification and drawings are objected to for the following reasons. Fig. 1 contains oligonucleotides that are not identified by a SEQ ID NO in either the figure or the brief description of the drawing. Appropriate correction is required, i.e. identification of the sequences in either the Figure or the brief description thereof.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

### *Written Description*

Claims 1, 4-14, 17-19, and 21-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 1, 4-14, 17-19, and 21-25 are drawn to methods and compositions comprising a nucleotide sequence from the genus of nucleotide sequences encoding a P.acnes lipase. A search of the art at the time the invention was filed suggests that there was only one known lipase from P.acnes, i.e. the extracellular lipase encoded by the P. acnes gehA gene (Miskin et al (1997) of record). However, one of ordinary skill in the art recognizes that microorganisms generally have more than one type of lipase. For example, mycoplasma genitalium comprises at least three types of lipase (see attached GenBank Accession Nos. AAC715551; Q49412; and A64238), and Bacillus subtilis comprises at least 3 types of lipases (see Kunst et al (Nature 390:249-256, 1997) at Table 1 under "METABOLISM OF LIPIDS", genes lipA, lipB, and ytpA). Thus one of skill in the art at the time of the invention would reasonably have expected P. acnes to have more than one type of lipase, such that the genus of nucleotide sequences encoding a P.acnes lipase would have comprise sequences other than that disclosed by Miskin (1997). This contention is supported by Bruggermann et al (Science 305: 671-673, (2004)) who recently disclosed the complete genome sequence of P. acnes and identified 15 open reading frames as encoding a "putative lipase/esterase" (see Table 1 at page 672). Bruggermann also noted that in addition to the extracellular lipase known in the prior art, 3 newly identified lipase/esterase genes encode a cell wall sorting signal, implicating them as extracellular lipases. GenBank accession Nos. AAT83525, AAT83749, and YP_055745, encoding a triacylglycerol lipase precursor, a lipase/acylhydrolase, and a putative lipase, respectively, are attached as evidence that the open reading frames disclosed by Bruggermann encode proteins of divergent

sequences, indicating high variability within the claimed genus. Note also that the claims embrace nucleic acids comprising sequences encoding "fragments" of lipase. This scope would likely include every conceivable PCR product that could be generated from the primers under any amplification conditions.

The specification does not disclose the sequence of any lipase. The disclosure of sequences is limited to three oligonucleotides that can be used to amplify a 1 kb sequence from P.acnes genomic DNA.

Applicant is referred to the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov). These guidelines indicate that a representative number of species may be disclosed by reduction to practice, description of complete structure, or identification of relevant identifying characteristics. Also, the guidelines indicate that in an unpredictable art, adequate written description of a genus that embraces widely divergent species cannot be achieved by disclosing only one species within the genus. See excerpt below:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus

In view of the fact that one of skill in the art at the time of the invention would have reasonably expected P.acnes to comprise more than one lipase, and the fact that P.acnes contains many lipase nucleic acid sequences that are separate and divergent from the single lipase gene disclosed in the prior art, one of skill in the art could not conclude that Applicant was in possession of the genus of nucleotide sequences encoding a P.acnes lipase, or fragments thereof, based on the disclosure of a PCR primers suitable for amplifying the P.acnes gehA coding sequence.

***Response to Arguments***

Applicant's arguments filed 6/23/04 have been considered as they apply to the ground of rejection set forth above, but are unpersuasive. Applicant argues at pages 10 and 11 of the brief that the specification reduces to practice nucleic acids encoding P.acnes lipase, and that designation of a gene as "P.acnes lipase" is sufficient for those of skill in the art to communicate the actual sequence of the protein because the sequence as reported in the literature and is immediately accessible. Applicant noted that as of the date of the response, there was no indication of naturally occurring variants of the polypeptide.

These arguments are unpersuasive because one of ordinary skill in the art appreciates that P.acnes must have more than one type of lipase, if for no other reason than because the P. acnes lipase known in the prior art is an extracellular lipase, and intracellular lipases are required for intracellular metabolism. As noted above, it was recognized prior to the time of the invention that other microorganisms had more than

one type of lipase. Finally after the invention was filed, Bruggermann demonstrated that P. acnes has as many as 15 putative lipases, four of which are extracellular. This would clearly indicate to one of skill in the art that Applicant was not in possession of the genus of nucleotide sequences encoding a P.acnes lipase at the time the invention was filed.

***Enablement***

Claims 1, 4-14, 17-19, and 21-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are two parts to this rejection. The first part deals with the enablement of intended uses implied by the claim term "vaccine", and enabled routes of administration. The second part deals with the scope of enabled nucleic acid sequences.

*Enablement of "vaccine"*

Nature of the invention and breadth of the claims.

Claims 1, 4-14, 17-19, and 21-23 are drawn to a "vaccine" comprising at least one nucleotide sequence encoding a P.acnes lipase. Stedman's Medical Dictionary defines "vaccine" as a preparation intended for active immunologic prophylaxis. So, the term "vaccine" is reasonably interpreted as a composition that is intended to protect an individual from contracting a disease, and claims 1, 4-14, 17-19, and 21-23 can be

interpreted as drawn to methods and compositions for protecting a person from contracting acne. It is noted that non-human animals do not suffer from acne, and in any event the specification does not contemplate the use of the claimed vaccine for any veterinary purpose. As such, enablement of the claimed "vaccine" depends on whether or not the specification teaches how to make it and use it in humans.

Claim 24 is a method of cosmetically improving the appearance of a person's skin who is suffering from acne vulgaris by administering a vector encoding a lipase or fragment thereof derived from P. acnes. As such, enablement depends on whether the specification teaches how to make and use the vector for use in humans to reduce the contribution of P.acnes to acne vulgaris, a disease which occurs only in humans.

Claims 19 and 25 are drawn to compositions. Claim 19 is a kit comprising a patch comprising one or more vectors comprising a nucleotide sequence encoding a P. acnes lipase or fragment thereof. Claim 25 is a composition comprising an adenovirus vector comprising a nucleotide sequence encoding a P. acnes lipase. The specification teaches no use for these compositions other than for the generation of an immune response for the purpose treating acne. No other real world use is envisioned for the compositions. As a result, enablement of the claimed compositions depends on whether one could use them as intended, i.e. to treat acne in a human.

Working examples and guidance in the specification.

The specification teaches a working example in which mice were vaccinated by intramuscular injection of an adenoviral vector encoding a P.acnes lipase, or a control adenoviral vector, and then challenged with intramuscular injection of P.acnes one

week after vaccination. Mice developed abscesses, and the experimental group showed a smaller abscess size relative to the control group. See Fig. 2. The specification does not disclose where in the animal any abscess was formed, and does not disclose whether or not the skin was colonized by P.acnes. Clarification of this issue is requested.

State of the prior art.

The prior art recognized the key to the problem of developing effective vaccines was to identify an antigen that can elicit the production of protective antibodies, such antibodies having the capacity to neutralize infectivity and thus protect the host against attack by a pathogen. (See Ellis, in Vaccines (Plotkin et al (eds.), W.B. Saunders publishers, Philadelphia, 1988, page 571, column 1, second full paragraph.) Also, Chandrasekhar et al (US Patent 6,248,329, issued 6/19/01) taught that "[A]lthough many investigators have tried to develop vaccines based on specific antigens, it is well understood that the ability of an antigen to stimulate antibody production does not necessarily correlate with the ability of the antigen to stimulate an immune response capable of protecting an animal from infection. As an example Feng et al (Inf. And Immun. 64(1): 363-365, 1996) taught that P55 is an immunogenic but nonprotective B. burgdorferi antigen in murine lyme disease.

The prior art taught the use of compositions comprising P.acnes bacteria and P.acnes bacterial derivatives as acne vaccines. See US Patent 4,057,627 to Stickl, which discloses the use of inactivated P. acnes as an oral vaccine for acne vulgaris. See e.g. claims 1-26, and column 8, lines 35-54. See also the discussion at column 1,

line 65 to column 2 line 13 which serves as a short review of the use of P.acnes as a vaccine. Although it was known in the prior art that P.acnes extracellular lipase was immunogenic in humans, a review of the prior art revealed no example of the use of P. acnes lipase as a vaccine. In fact, Ingham et al (Brit. J. Dermatol. 116: 805-812, 1987) taught that there was no difference in the prevalence or titre of antibodies to P. acnes lipase when patients with severe acne were compared with normal controls, (see summary and Table 4 at page 810). This suggests that P.acnes lipase is not an antigen that provides a protective immune response in humans.

Although the specification demonstrates that a protective immune response against P.acnes can be generated in mice that have been immunized against a P.acnes lipase, a search of the prior art indicated that the mouse has not been established as an accepted animal model of acne. No citations were discovered in which a mouse was used to study acne lesions such as those described in the instant specification, and Kearney et al (J. Gen. Microbiol. 2431-2437, 1982) taught that P.acnes is absent from mouse skin (see abstract). It is noted that De Young et al (J. Inv. Derm. (8345): 394-398, 1 1/1984) developed a rat model for acne by injection of P.acnes into the ear of the animal. However, Whyte et al (J. Comp. Pathol. 122 (2-3): 17-184, 4/2000) taught that while some animal models mimic certain aspects of acne, few represent the chronic nature of the response seen in the human. Whyte notes that the system of De Young was limited because only histological assessments were made and only a few sites per animal could be tested (page 177, column 2, lines 3-12). Whyte further notes that rodent skin is dissimilar to human skin in terms of its histology, chemical composition,

permeability and arrangement of hair follicles and pilosebaceous glands, and for these reasons the pig is a superior model (page 178, lines 14-19). Brummitt et al (in Skin Models: Models to study function and disease of skin, 1986) suggested that the lack of animal models for investigating bacterial involvement in acne was due to the fact that the bacterial flora is quite different in animals, and noted that the host response to different microbiological stimuli may differ between species. Thus it is not clear that an antigen that provides a protective response in a mouse will also provide a protective response in a human due to differences in skin physiology and immune response.

McCluskie et al (Molecular Medicine 545: 287-300, 1999) studied the relevance of animal models of genetic immunization to treatment of disease of human disease, as well as the effects of the routes of administration of DNA vaccines on the quality of any resulting immune response. McCluskie taught that promising results in animal models have not been realized in human trials and considerable effort is now being focused at understanding this difference and developing ways of improving the efficacy of DNA vaccines." See final sentence of first paragraph on page 288, column 1. McCluskie points out that the strength and nature of immune responses in mice treated with DNA vaccines appear to be influenced by a number of factors; however, these variables may not be of similar importance in larger animals including humans. As such, optimization methods developed in mice may not necessarily be applicable to humans. See page 288, column 2, first full paragraph. In fact, it is clear that some vaccines developed in mice do not function at all in some primates. At page 296, column 2, second full paragraph, McCluskie states that "[t]he realization that results in mice often do not

predict the situation in humans also led to a large number of DNA vaccine studies in non-human primates, including Aotus monkeys [citation omitted], rhesus monkeys [4 citations omitted], and chimpanzees [6 citations omitted]. IM injection of plasmid DNA vaccines, while highly immunogenic in mice was found to be only relatively so in chimpanzees and essentially not at all in Aotus monkeys [citation omitted]. Furthermore, although early human studies have demonstrated the safety and potential of DNA vaccines, results obtained have not been as good as predicted from animal models [4 citations omitted]. Collectively, these results indicate that no animal model may be ideal for prediction of efficacy in humans." McCluskie concludes that 'it is difficult to predict from mouse studies the potential of a new vaccine in humans. In fact, in those human trials that have been carried out, none of the DNA vaccines induced the strong immune responses that had been seen in mice with the same vectors. Furthermore, although non-human primate models are frequently used for development and testing of human vaccines, it is not clear how predictive they will be in the case of DNA vaccines where efficacy, by virtue of the requirement to first transfect cells and express antigens, relies on many factors other than immunological responses to the antigen. We will not know the answer to this until after greater experience has been achieved in non-human primates and human clinical trials." Thus the success in primates of vaccines developed in mice is considered by those of skill in the art to be unpredictable.

Regarding the route of administration of the vaccine, McCluskie taught that this variable "influences the strength and nature of immune responses in mice and non-human primates. However, the results in mice were not always predictive of those in

monkeys and this is likely true for humans as well. Optimal dose and immunization schedule will most likely vary between species. It is not clear whether results in non-human primates will be predictive of results in humans thus additional studies are required." McCluskie tested eight injection-mediated routes including intravenous, intramuscular, subcutaneous, and intraperitoneal, six non-injection routes including inhaled and oral routes, and one transcutaneous route (gene gun). The results indicated that whereas substantial immune responses were obtained by IM, IV, sublingual, and intradermal injection, as well as by gene gun, none of the non-injection routes gave rise to any antibodies. See abstract, and Fig. 1 on page 291. This is objective evidence that the route of DNA delivery influences the immune response obtained in genetic immunization, and that the results obtained by oral and inhalation routes are unpredictable.

In summary, the state of the art of immunization suggests that it is generally unpredictable which antigens will provide a protective or preventive immune response, the significance of results in the disclosed animal model are unknown because it is not an art recognized animal model of human acne, and it is recognized that genetic immunization of mice may not be predictive of results in primates. Furthermore, although P.acnes extracellular lipase is known to be antigenic in humans, there is no difference in the prevalence or titre of antibodies to P. acnes lipase when patients with severe acne were compared with normal controls, so it appears that antibodies to P.acnes lipase do not provide a protective immune response in humans. The specification fails to provide any technical guidance that would improve the state of the

art of genetic immunization in general, and therefore does not reduce the unpredictability associated with genetic immunization in general, or with P.acnes lipase immunization specifically. Given the state of the art, the unpredictability of the art, the level of exemplification, and the teachings in the specification, one of skill in the art would have to perform undue experimentation in order to practice the invention commensurate in scope with the claims.

If Applicant is able to overcome this portion of the rejection, the following portion will still apply.

*Scope of nucleic acids*

Instant claims 1, 4-14, 17-19, and 21-25 are drawn to a nucleotide sequence encoding a P.acnes lipase. The specification discloses 3 oligonucleotides that can be used to amplify from P. acnes genomic DNA a 1 kb DNA from the P.acnes geh A gene that encodes a lipase. The specification does not disclose the sequence of the amplified PCR product, but the disclosed oligonucleotides are suitable for amplifying the lipase sequence disclosed by Miskin (1997), e.g. Fig. 2 on page 1748. A search of the prior art indicates that, at the time the invention was filed, no other P.acnes lipase nucleic or amino acid sequence was known. However, as discussed above, one of ordinary skill in the art at the time of the invention would have recognized that microorganisms generally have more than one type of lipase. For example, Mycoplasma genitalium and Bacillus subtilis each comprise at least 3 types of lipases. Thus one of skill in the art at the time of the invention would reasonably have expected P. acnes to have more than one type of lipase. This contention is supported by

Bruggermann (2004) who recently disclosed the complete genome sequence of P. acnes and identified 15 open reading frames as encoding a "putative lipase/esterase" (see Table 1 at page 672). Bruggermann also notes that in addition to the extracellular lipase known in the prior art, 3 newly identified lipase/esterase genes encode a cell wall sorting signal, implicating them as extracellular lipases.

The specification fails to enable the full scope of the invention as claimed because it does not disclose any nucleotide sequence encoding a P.acnes lipase, even though the claims can be reasonably interpreted as embracing nucleic acid sequences encoding *any* P. acnes lipase, or fragment thereof, and one of skill in the art would have reasonably expected there to be more than one P.acnes lipase. The specification provides no guidance as to how to isolate any P.acnes lipase other than the lipase disclosed by Miskin (1997). This amounts to the omission of essential subject matter required for the practice of the full scope of the invention. While Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the invention. In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must

supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

Clearly the nucleic acids required for the practice of the invention are critical elements that cannot be overlooked in the process of providing an enabling disclosure. Because the specification fails to teach how to make any nucleic acid encoding a P.acnes lipase, other than the one encoded by the one 1b PCR fragment generated by the disclosed primers, the specification is enabling only for nucleic acids encoding that one lipase, and one of skill in the art at the time of the invention would have had to perform undue experimentation in order to make a nucleic acid encoding any other P.acnes lipase.

***Response to Arguments***

Applicant's arguments filed 6/23/04 have been considered as they apply to the ground of rejection set forth above, but are unpersuasive.

Applicant asserts at pages 4 and 5 of the response that the claims have previously been construed too broadly by the Examiner, and have been amended to clarify that the intended use of the vaccines is to generate an immune response. Applicant argues that because the methods and compositions are capable of achieving this result, they are enabled. This is unpersuasive in the context of claims 1, 4-14, 17, 18, and 21-24 because these claims require that the effective agent in the compositions and methods is a "vaccine". As discussed above, this represents an intended use that the specification does not enable, i.e. a prophylactic effect in humans. Applicant notes at page 4 that claims 19 and 25 are drawn to compositions without any functional

language, and should not be included in a rejection based on such language. This is unpersuasive because the specification fails to satisfy the "how to use" prong of the enablement requirement because it teaches no real world use for these compositions other than the treatment of acne in a human.

Applicant argues at pages 5-10 that the McCluskie reference is flawed and does not support a finding of a lack of enablement.

At pages 6, 8, and 9 Applicant notes that claims 5, 6, and 18 are limited to virus-based vaccines, whereas McCluskie considers naked DNA vaccines. Applicant argues that McCluskie cannot be relevant to these virus-based claims. This argument is unpersuasive because it is a statement of opinion that is unsupported by evidence. Applicant has presented no evidence that the results of McCluskie would not also be applicable to viral genetic vaccines. Furthermore, as stated in the rejection above, it is entirely unpredictable as to whether or not P.acnes lipase would provide a protective immune response in humans in view of the fact that Ingham (1987) taught that there was no difference in the prevalence or titre of antibodies to P. acnes lipase when patients with severe acne were compared with normal controls , (see summary and Table 4 at page 810).

Applicant argues at pages 5-10 of the response that the results of genetic immunization of mice are predictive of similar responses from humans.

Applicant asserts at page 5 that McCluskie comprises flaws as pointed out at pages 12 and 13 of the response to final rejection. A review of these pages shows that Applicant considers one flaw in McCluskie to be that disproportionately large dosage

and injection volumes are used relative to those that would be used in humans, so that the results in mouse and human studies cannot be easily compared. Applicant concluded that the results of McCluskie cannot substantiate the view that mice immune responses to DNA vaccines do not preduct similar results in humans.

It is unclear how this alleged flaw affects the position taken by McCluskie that mouse studies are not necessarily predictive of human results. McCluskie states that "[t]he realization that results in mice often do not predict the situation in humans also led to a large number of DNA vaccine studies in non-human primates, including Aotus monkeys [citation omitted], rhesus monkeys [4 citations omitted], and chimpanzees [6 citations omitted]. IM injection of plasmid DNA vaccines, while highly immunogenic in mice was found to be only relatively so in chimpanzees [4 citations omitted] and essentially not at all in Aotus monkeys [citation omitted]. McCluskie further states that "in those human trials that have been carried out, none of the DNA vaccines induced the strong immune responses that had been seen in mice with the same vectors." The position that the results in mouse studies do not allow extrapolation to humans is based upon McCluskie's analysis of the prior art which is documented with at least 5 references from the scientific literature. The results obtained in McCluskie have no effect on this fact that the results obtained in mice cannot be routinely extrapolated to humans, particularly in the absence of an art-recognized model of the disease in question.

Applicant argues at page 7 that others of skill in the art did not share the opinions expressed by McCluskie. For support Applicant relies Gerdts (2000), and Tackett

(1999), which were addressed completely in the Final Rejection, and on US Patents 6,696421, 6,284,533, and 6,451769. These references show that those of skill in the art previously used animal models to test vaccines prior to administration to humans. The Gerdt's reference does not pertain to a mouse animal model, but uses sheep instead. The Tackett reference shows that a vaccine tested in mice was subsequently used in a phase 1 trial, and does not report significant positive results in humans. The cited patents are considered to be enabled, but Applicant is reminded that each application is prosecuted on its own merits. It is not the Office's position that no vaccine tested in a mouse model ever worked in a human. The Office's position is that the mouse model used by Applicant is not an art recognized model, and that the prior art indicates that one cannot predictably extrapolate the results from mouse studies to humans. When combined with the fact that it is at best unpredictable as to whether or not lipase will act as a protective antigen, it becomes clear that the specificaiton fails to enable the claimed vaccine.

At the paragraph bridging pages 7 and 8, Applicant attacks the credibility of McCluskie. Applicant asserts that the existence of over 500 clinical trials based on transfection and expression of foreign genes proves that those of skill in the art consider transfection and expression of foreign genes in humans feasible. The Office doubts that McCluskie would argue that it is unfeasible to express foreign genes in humans. The passage to which Applicant refers is merely an attempt by McCluskie to provide an explanation for the objective fact that the results of mouse DNA vaccine studies are frequently not repeatable in larger animals. It is unclear how any number of clinical

trials of human gene therapy affect this objective fact. It is because we cannot extrapolate directly from animal models to humans that clinical trials exist. If the results of mouse studies were sufficient, there would be no need for clinical trials. The Office also points out that the unpredictability of the claimed invention also involves the fact that the animal model is not a recognized model of acne, and that there is no apparent reason to believe that lipase will be a protective immunogen in humans.

At pages 9 and 10 of the response, Applicant considers the animal model, referring to pages 16-18 of the response to final rejection. At page 16-18 of the response to final rejection, Applicant argues that given the long practiced use of mice in immunology studies, the results in Example 2 would be expected in humans. This is unpersuasive because it does not address the facts that the animal model is unrecognized, mice do not suffer from acne, and that the prior art shows that normal and acne-suffering individuals have similar titres of lipase antibody, indicating that the antibody is not protective. Applicant's argument that whole P.acnes vaccines exist does not provide any support or evidence that lipase will be a protective antigen. P.acnes comprises thousands of antigens and there is no reason to conclude that lipase provides a protective immune response. As discussed above, the available evidence suggests that it does not provide such a response in humans.

Applicant argues that antibodies that inhibit lipase might interfere with growth of P.acnes, relying for support on the previously considered declaration of Dr. Kumar. Although it is clear that antibodies that inhibit the activity of a P.acnes lipase can be produced in humans, Dr. Kumar's declaration provides no evidence that such antibodies

will inhibit the growth of P.acnes, or that inhibition of such growth would provide prophylaxis as implied by the term "vaccine". Instead the supporting material on which Dr. Kumar relies states that lipase is a "possible colonization factor" (Gribbon, 1993), and that there is a correlation between free fatty acids and P.acnes colonization (Kearney, 1984). The Higaki reference is unclear, but seems to suggest that certain drugs suppress P.acnes growth (as measured by propionic acid concentration) more than they inhibited lipase activity (measured by butyric acid production), seemingly indicating that the drugs worked by a mechanism other than lipase inhibition. As stated in the Advisory action of 12/29/03 . Applicant has presented no evidence that the results in the mouse model can be extrapolated to humans, i.e. that the model used is an accepted animal model, or that the differences between mouse and human physiology discussed in the rejection are insignificant in the context of the invention. In viewof the forgoing, the rejection is deemed proper.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 7, 10-12, 21, and 24 rejected under 35 U.S.C. 102(b) as being anticipated by Stickl (US Patent 4,057,627, 1 1/8/1977), as evidenced by Taveme et al (Infection and Immunity 3743:927-934 (9/1982).

Stickl teaches compositions comprising attenuated P.acnes and their use as oral vaccines for acne vulgaris. See e.g. column 4, lines 12-16, column 8, lines 35-54, and claims 1-26. Note that Stickl refers to "corynebacterium acnes", rather than P.acnes. The designation "corynebacterium acnes" was changed to P.acnes after the publication of Stickl, so one of skill in the art appreciates that Corynebacterium acnes and P.acnes are the same organism. See e.g. Taveme et al (abstract). The Stickl disclosure anticipates instant the claims because inactivated P.acnes is considered to be a vector comprising nucleic acids encoding all P.acnes antigens, including P.acnes lipases. The vaccine may be aqueous as required by instant claim 21. See abstract.

***Response to Arguments***

Applicant's arguments filed 6/23/04 have been considered as they apply to the ground of rejection set forth above, but are unpersuasive.

Applicant argues at pages 11 and 12 of the response that the claim term "vector" is defined as a genetically engineered nucleic acid construct. The Office agrees that this definition is embraced by the claims. However, Applicant's attention is directed to the sentence bridging pages 8 and 9 of the specification which indicates that the definition referred to above is not limiting. As such, "vector" is given its broadest reasonable interpretation, which includes genetic vaccines such as that of Stickl. Note that, as previously mentioned, bacterial vectors are referred to in the art as genetic vaccines. See e.g. Merz (JAMA (1987) 258(15):2028).

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.